as they were "preselected" based on prior model-fitting exercises. In the present case, the knot values were determined through model fitting with NIOSH data (e.g., maximization of the likelihood of the model for best fit to the lymphoid cancer data), and thus are obviously estimated parameters (*k*) in the analysis. That is, for the spline models, the parameters (*k*) estimated by USEPA were clearly: (1) the "knot" value; (2) the slope above the knot; and (3) the slope below the knot (*k*=3). However, USEPA (2016) did not account for statistically estimating the optimized knot value. Thus, it appears the degrees of freedom (*df*) were inappropriately enlarged for the spline models (i.e., *df=data points modeled (n)-k*), which was not inconsequential. Among other consequences, this:

- Inappropriately decreased the p-value for adequate statistical fit, incorrectly implying that the linear two-piece spline model with a knot at 1,600 ppm × days for lymphoid cancer fit the data statistically better than other models in Table 4-6 of USEPA (2016); and
- Inappropriately decreased the Akaike information criterion (AIC) for the spline models, which did not allow for an appropriate comparison of model fit among models for either lymphoid cancer or breast cancer incidence.

Thus, this appears to amount to an unfortunate statistical misevaluation of model fit in USEPA (2016). Appendix D of USEPA (2016), a revised report of Dr. Kyle Steenland submitted in 2010 under contract with USEPA, acknowledges this *df*/p-value issue but then argues for the log-linear two-piece spline model (not ultimately selected by USEPA) not based on statistical fit criteria, but rather conformance with the categorical and cubic spline models in the low-exposure region and the nearly linear exposure-response relationship in that region (p. D-13 of USEPA 2016). In regard to the linear two-piece spline model ultimately selected by USEPA (2016), Section 3.4.1.2.2.3 demonstrates how it statistically significantly over-estimates risk for every cumulative exposure group, including the lowest (see Figures 9-12).

In regard to the first bullet above, an example in Appendix 5 demonstrates that a p-value of 0.15 is the correct p-value for the likelihood ratio test (not 0.07 as in Table 4-6 of USEPA 2016) when appropriately using *k*=3 for the log-linear two-piece spline model with a knot at 1,600 ppm × days (lymphoid cancer). Similarly, for the linear two-piece spline model with a knot at 1,600 ppm × days (lymphoid cancer) ultimately selected in USEPA (2016), the correct p-value is 0.14 (not 0.07 as in Table 4-6 of USEPA 2016*). Thus, the correct p-values indicate that the likelihoods of these two-piece spline models (linear and log-linear) with knots at 1,600 ppm × days are not different from the likelihood of the null model at the 5% significance level* (i.e., the fitted two-piece spline models do not explain the variability in the data statistically significantly better than the null model). *The same is true for all two-piece spline models in Table 4-6 of USEPA (2016) when appropriately using k=3 (p-value range of 0.11-0.15), putting the two-piece spline models and the log-linear (standard Cox regression) model on equal ground in this regard*

(Appendix 5), although the linear two-piece spline assessment selected in USEPA (2016) statistically significantly over-predicts lymphoid cancer risk whereas the TCEQ's log-linear model does not over- or under-predict risk (see Section 3.4.1.2.2.3, Figure 8, and Appendix 3).

Regarding the second bullet, the USEPA SAB does not comment on or examine this specific AIC issue in Appendix H of USEPA (2016). *The SAB does recommend less reliance on the AIC* (e.g., pp. I-2 and I-9 of USEPA 2016), *particularly its naïve use without other scientific considerations* (pp. I-17 and I-18 of USEPA 2016), and discusses the true fixing of some model parameters (*as opposed to statistical fitting/estimating parameter values from the data as USEPA did*) in a more general discussion of model parsimony (p. I-16 of USEPA 2016). However, Appendix 5 of this DSD contains an example showing that an AIC of 464.6 is the correct AIC value (not 462.6 as in Table 4-6 of USEPA 2016) when appropriately using k=3 for the log-linear two-piece spline model with a knot at 1,600 ppm × days (lymphoid cancer). Similarly, for the linear two-piece spline model with a knot at 1,600 ppm × days (lymphoid cancer) ultimately selected in USEPA (2016), the correct AIC is 464.5 (not 462.1 as in Table 4-6 of USEPA 2016). *Consequently, not only does the linear two-piece spline model for lymphoid cancer ultimately selected by USEPA (2016) not explain the variability in the data statistically significantly better than the null model, but the correct AIC value (464.5) is higher than those for all log-linear (Cox regression) and linear models in Table 4-6 of USEPA (2016). Again, as a related issue, USEPA's selected model assessment for lymphoid cancer mortality statistically significantly over-estimates risk (e.g., Figure 8 and Figures 9-12).* Appendix 5 also contains an example showing that an AIC of 1,956.360 is the correct AIC value (not 1,954.360 as in Table 4-14 of USEPA 2016) when appropriately using k=8 for the linear two-piece spline model with a knot at 5,750 ppm × days (breast cancer incidence) ultimately selected in USEPA (2016). Thus, the correct AIC for the linear two-piece spline model (1,956.360) is higher than or similar to AIC values for the log-linear (Cox regression) and linear models in Table 4-14 of USEPA (2016), with the same being true for the AIC value (1,956.485) for the log-linear two-piece spline model. These two-piece spline model AIC values (for breast cancer incidence) are very similar to the AIC for the standard Cox regression model (1,956.675), which also has a p-value <0.5, putting them on par with each other in this regard (Appendix 5).

As visual fit to the data was also used as a criterion for model selection (e.g., pp. 4-66 and 4-100 of USEPA 2016), the second issue concerns the apparent unintentional visual misrepresentation of model fit in Figures 4-3 and 4-8 of USEPA (2016). Most simply, no true visual comparison of model fit to the data can be made based on Figures 4-3 and 4-8 (pp. 4-21 and 4-51 of USEPA 2016) since the data shown are not the data to which the models shown were fit. The actual data underlying model fits shown are the individual data, not the less refined categorical data shown in the figures. *Thus, because the model fits shown in Figures 4-3 and 4-8 are those to the individual data (and not the categorical data depicted), the figures do not actually show model fit to the modelled data at all.* For lymphoid cancer, objective examination of the model fits to

the underlying data reveals no readily apparent superior fit by any particular model (Appendix 6). Unfortunately, the NIOSH breast cancer incidence data are not publicly available, and to the TCEQ's knowledge no graph similar to that in Appendix 6 for lymphoid cancer has been produced to enable an appropriate visual examination of model fits to the actual underlying breast cancer incidence data.

The above statistical and visual fit considerations do not constitute the type of strong data (e.g., robust mechanistic understanding and justification) needed to justify a supra-linear dose-response model (i.e., the steep lower-dose slope component of USEPA's linear two-piece spline model) for low-dose extrapolation for EtO (TCEQ 2015). In summary:

1) Correct p-values for the two-spline models for lymphoid cancer mortality are *within the range* of those for the linear and log-linear (Cox regression) models, although correct AIC values for the two-spline models are *slightly higher* than those for the linear and log-linear (Cox regression) models;
2) Correct AIC values for the two-spline models for breast cancer incidence (1,956.360-1,956.485) are *higher than or similar to* those for the linear and log-linear (Cox regression) models, with p-values for Cox regression models also <0.05;
3) *Thus*, even outside of the lack of the critical deterministic (e.g., mechanistic) data needed to support use of an overall supra-linear model, *as a peripheral matter there appears to be no strong statistical indication of a need to adopt a non-conventional, supra-linear model over a more standard model*; and
4) As might be expected based on 1 and 2, visual examination of the model fits to the underlying data for lymphoid cancer reveals no readily apparent superior fit by any particular model.

These circumstances do not support deviation from more standard/conventional dose-response models (e.g., Cox proportional hazards model).

3.4.1.4 Selection of the Extrapolation Model

3.4.1.4.1 Conclusions on Use of USEPA's Linear Two-Piece Spline Model

The following summarizes the TCEQ's conclusions about the USEPA's linear two-piece spline model for use in the derivation of a URF for EtO. The TCEQ (2015) guidelines require sufficient mechanistic or biological data to support the application of a supra-linear model (i.e., its steep slope beginning at zero dose). *However, adoption of an overall supra-linear model (i.e., the steep lower-dose component) for EtO low-dose extrapolation is not justified based on mechanistic data or supported by other considerations described above (e.g., key epidemiological data, model ground-truthing).* For example, the model assessment ultimately

selected by USEPA (i.e., the upper bound of the linear two-piece spline model with the "knot" at 1,600 ppm × days, 15-year exposure lag) has been demonstrated to statistically significantly over-estimate the total number of lymphoid cancer mortalities observed for the NIOSH cohort as a whole (e.g., predicting 141 compared to the 53 actually observed) as well as for every cumulative exposure group (Appendix 3).

The TCEQ's conclusion that relevant considerations do not provide a sufficient scientific basis for the application of an overall supra-linear model (i.e., its steep low-dose slope) for low-dose extrapolation *is consistent with USEPA (2016) acknowledging that reasons (biological, mechanistic, or otherwise) supporting a supra-linear dose-response are unknown, stating to the SAB "the EPA is not aware of a mechanistic explanation" (p. I-29 of USEPA 2016; also see pp. I-34 and 4-71).* In fact, considerations herein suggest that sub-ppb EtO exposure concentrations (e.g., 0.0001-0.01 ppb) may not be consistent with the production of excess (i.e., above background) risk. By contrast, progressively higher EtO air concentrations that produce total internal exposures (endogenous + exogenous) progressively higher than the normal endogenous range are considered more likely to be associated with excess (i.e., above background) risk as the body's normal detoxification and repair processes for endogenous EtO become progressively more likely to be less efficient and/or overwhelmed. For example, a continuous EtO air exposure concentration that itself produces an internal dose above the normal endogenous range is considered most likely to be associated with excess risk (e.g., ≥ ≈4.6-7 ppb; Table 4 of Kirman and Hays 2017), followed by EtO air concentrations that themselves produce internal doses similar to the upper end of the normal endogenous range (e.g., continuous exposure concentrations of 3.5-6.9 ppb would be expected to produce internal doses approximating the 90^{th} to 99^{th} percentile of the normal endogenous range; Table 4 of Kirman and Hays 2017).

USEPA provides no robust biological or mechanistic basis for adopting an overall supra-linear EtO dose-response (i.e., the linear two-piece spline model). In fact, biological/mechanistic considerations by USEPA (2016) are essentially limited to:

1) Choosing between two "knot" values for the two-piece spline models, wherein the agency simply indicates that a knot at…
    a. 1,600 ppm × days (compared to 100 ppm × days) results in a more "biologically realistic" exposure-response for lymphoid cancer as it results in a more gradual rise in low-dose risk and a more plausible rise at higher exposures (p. 4-16 of USEPA 2016); and
    b. 5,750 ppm × days results in a more "biologically realistic" general model shape for breast cancer incidence (p. 4-52 of USEPA 2016).

2) Considering "biologically plausible" exposure lag periods (e.g., pp. D-6 and D-38 of USEPA 2016), although the USEPA SAB did not find USEPA's biological argument to be strong even for this limited purpose (p. I-1 of USEPA 2016).
3) Citing direct mutagenic activity as mechanistic justification for typical default linear low-dose extrapolation (pp. 4-22, 4-37, 4-54, 4-61, 4-74, 4-94, C-30, and I-31 of USEPA 2016).

In acknowledging the lack of mechanistic data for EtO to support the biological plausibility of a supra-linear dose-response, USEPA cites *"insufficient information to elucidate a basis"* (p. I-34 of USEPA 2016). USEPA further indicates that "it is unclear how the available biological data can be used to guide general model selection" (p. I-31 of USEPA 2016). In addition to USEPA's acknowledgment of a lack of a mechanistic and/or biological justification, all the considerations discussed by the TCEQ in various sections above (e.g., MOA, reality checks of model predictions) consistently support the conclusion that there is a lack of data to adequately support the application of the steep low-dose slope of a supra-linear model to extrapolate to significantly lower doses. *The statistical demonstration of the significant over-estimation of lymphoid cancer mortality by the model assessment selected by USEPA (i.e., the upper bound of the linear two-piece spline model with the "knot" at 1,600 ppm × days, 15-year exposure lag) is of particular interest and does not lend scientific credibility to the associated USEPA (2016) EtO URF.*

Without a solid mechanistic basis, USEPA (2016) is primarily left with the "appearance" of supra-linearity based on a less than accurate representation of model fit. The TCEQ considers model fit criteria as a matter secondary to consideration of the critical deterministic (e.g., mechanistic) data needed to support adoption of a supra-linear model (TCEQ 2015). Regardless, *when appropriately considering statistical and visual model fit, the TCEQ finds no strong (much less compelling) statistical or visual indications of a need to adopt a non-conventional, supra-linear model over a more standard model* (see Section 3.4.1.3 and Appendix 6). Moreover, *the underlying key epidemiological data cannot support the application of a supra-linear model (i.e., the steep low-dose slope) for extrapolation to low environmental EtO doses since the data are not informative as to the shape of the dose-response curve at the truly low doses of interest* (e.g., in the range of typical environmental concentrations). The TCEQ's conclusions about model fit and that the key epidemiological data are not informative as to the shape of the dose-response curve at the low environmental EtO doses of regulatory interest are consistent with USEPA acknowledging that the model and low-dose extrapolation (as well as exposure estimation) are primary sources of uncertainty and *"the actual exposure-response relationship at low exposure levels is unknown"* (pp. 4-61 and 4-74 of USEPA 2016).

High-dose carcinogenicity data alone are incapable of informing truly low-dose risk, no matter how extensive the analyses or peer review (i.e., other relevant information such as mechanism/MOA must be duly considered). *USEPA (2016) should not have based a URF on a*

supra-linear model (i.e., its lower-dose component) without a robust mechanistic justification for expecting the associated steep low-dose slope component to be applicable at truly low doses or used it to make a large low-dose extrapolation across the endogenous range (and below) considering that the agency actually considers sublinearity as "highly plausible" in this range. The key study used by USEPA does not provide EtO dose-response data anywhere near environmental levels/doses. USEPA (2005a) recognizes that the relatively small exposure range observed in many epidemiologic studies makes it difficult to discern the shape of the exposure- or dose-response curve, which in the present case concerns the range being limited to only very high exposures. USEPA (2016) acknowledges that *points of departure are substantially above typical EtO environmental levels, resulting in uncertainty in risk at environmental levels* (p. I-14 of USEPA 2016). For example, the agency cites a POD for breast cancer incidence (12 $\mu g/m^3$ or 6.6 ppb) that is almost 3,000 times higher than the cited average background level (0.0044 $\mu g/m^3$ or 0.0024 ppb) and further acknowledges that the two lowest deciles have RRs < 1 and thus "are not by themselves consistent with the unit risk estimate." *Based on the considerations discussed in this DSD (e.g., MOA, normal endogenous levels, model reality checks), the TCEQ finds the assessment to follow to be much more biologically and scientifically reasonable.*

In summary, *robust mechanistic and/or biological data adequate to justify use of an overall supra-linear model (i.e., the application of the steep lower-dose slope for low-dose extrapolation) do not exist for EtO in this case*. In fact, relevant considerations strongly suggest that use of such a model (e.g., USEPA's linear two-piece spline model) for low-dose extrapolation is inappropriate (see the discussions above). As the adoption of supra-linear modeling results (i.e., the steep slope beginning at zero dose for low-dose extrapolation) is scientifically unjustified, the corresponding analyses in USEPA (2016) are considered no further in this DSD for potential adoption by the TCEQ.

3.4.1.4.2 Conclusions on Use of an Alternative Model

Based on the considerations discussed above (e.g., MOA, model ground-truthing), *the TCEQ has determined that a low-dose extrapolation model for EtO carcinogenicity that is no more than linear overall is both reasonable and justified*, especially if such extrapolations result in EtO air concentrations (e.g., at 1E-05 excess risk) corresponding to internal exposures within the normal endogenous background range where USEPA (2016) states that a sublinear dose-response is highly plausible. *The Cox proportional hazards model is one such model that has been used previously by the TCEQ* (e.g., in the 1,3-butadiene carcinogenic assessment; TCEQ 2008) and was considered by USEPA (2016). In their assessment of EtO carcinogenicity, Valdez-Flores et al. (2010) also use the Cox proportional hazards model with a default lifetime value of 70 years, consistent with TCEQ guidelines (TCEQ 2015). Additionally, USEPA (2016) describes the Cox proportional hazards model as sublinear at low doses, which would conform to dose-response shape expectations (unlike a strictly linear low-dose model) if risk-based EtO air concentrations (e.g., at 1E-05 excess risk) ultimately correspond to doses in or below the

normal endogenous range. *Based on the considerations discussed above, the TCEQ selects the Cox proportional hazards model for the carcinogenicity assessment of EtO.* Additional discussion of the Cox proportional hazards model relative to other models considered by USEPA (2016) and the TCEQ for lymphoid cancer mortality and breast cancer incidence can be found in Appendix 5. *Lastly, information in Section 3.4.1.2.2.3 and Appendix 3 demonstrates that the Cox proportional hazards model adopted by the TCEQ neither significantly over- or under-predicts lymphoid cancer mortality for the NIOSH cohort as a whole or for any cumulative exposure group.*

3.4.1.5 Relevant Cox Proportional Hazards Model Results

In accordance with the section above, Cox proportional hazards modeling results were reviewed. For example, Table 6 provides maximum likelihood estimate (MLE) results from Valdez-Flores et al. (2010) for various potential cancer endpoints. *This DSD considers the same critical cancer endpoints as USEPA (2016), namely lymphoid and breast cancer.* The TCEQ will ultimately evaluate excess risk results for biological plausibility and scientific reasonableness in the context of relevant information such as normal endogenous levels, associated predicted background rate, etc.

Table 6: Cancer Endpoint-Specific Environmental EtO Air Concentrations at 1 in 100,000 Excess Risk based on Maximum Likelihood Estimates (MLE) (Valdez-Flores et al. 2010) [a,b,c]

Cancer Endpoint	1E-05 Air Level based on MLE for NIOSH: Males (ppb)	1E-05 Air Level based on MLE for NIOSH + UCC: Males (ppb)	1E-05 Air Level based on MLE for NIOSH: Females (ppb)	1E-05 Air Level based on MLE for NIOSH: Males + Females (ppb)	1E-05 Air Level based on MLE for NIOSH + UCC: Males + Females (ppb)
Lymphoid Tumors [d]	6	10	-ns	8	15
Breast Cancer [d,e]	-ns	-ns	7	17	17
Lymphohematopoietic Tissue [f]	6	10	-ns	9	19
Non-Hodgkin's Lymphoma	12	17	-ns	15	23
Lymphocytic Leukemia	13	16	-ns	19	24
Leukemia	18	23	-SS	78	92
Central Nervous System	-ns	-SS	28	-ns	-ns
Malignant Brain	-ns	-ns	19	-ns	-ns
Pancreatic	-ns	-ns	12	-ns	-ns

[a] Environmental air concentration = occupational concentration × 240 days/365 days × 10 m^3/20 m^3; no occupational exposure lag.
[b] USEPA (2005) age-dependent adjustment factors incorporated.
[c] An EtO air concentration (ppb) value in a cell indicates that the estimated slope was positive for mortality with cumulative ethylene oxide exposure for the cancer endpoint in the NIOSH cohort, though none were statistically significantly positive, while the slopes for other endpoints in the NIOSH cohort were negative (denoted by "-ns") and some even statistically significantly negative (denoted by "-SS").
[d] Cancer endpoint used by USEPA (2016), includes non-Hodgkin's lymphoma, multiple myeloma, and lymphocytic leukemia as developed in Steenland et al. (2004).
[e] One male breast cancer mortality in the NIOSH cohort; none in the UCC cohort.
[f] Includes leukemia (and specifically myeloid and lymphocytic leukemia), non-Hodgkin's lymphoma, and multiple myeloma.

The results in Table 6 do not incorporate any exposure lag, while USEPA (2016) ultimately utilizes an exposure lag of 15 years. Therefore, in preparing this DSD, the TCEQ contracted with the first author on the Valdez-Flores et al. (2010) study to provide exposure-lagged results for lymphoid and breast cancer mortality that had been previously developed in the course of his research.

3.4.1.5.1 Parameter Estimates

3.4.1.5.1.1 Lymphoid Cancer

Tables 7, 8, and 9 contain log-linear (Cox regression) model results for lymphoid cancer mortality in the NIOSH (male + female), NIOSH (male only), and UCC (male only) cohorts, respectively, at various EtO exposure lags. The UCC results are based on an update of the cohort through 2013 that is not yet published.

Table 7: Lymphoid Cell Lineage Tumor Mortality - NIOSH (male + female) - MLE and Standard Error (SE) of the Estimate for Different EtO Exposure Lags

Lag (years)	MLE	(SE)	Deviance [a]: -2 × Ln(Likelihood) (p-value vs null) [b]	Likelihood Ratio Test Statistic: Deviance (null model) – Deviance (model) (p-value vs zero lag) [c]
0	3.48×10^{-6}	(1.83×10^{-6})	726.188 (0.1088)	2.571 (n/a)
5	3.45×10^{-6}	(1.95×10^{-6})	726.495 (0.3224)	2.264 (1.0000)
10	3.11×10^{-6}	(2.23×10^{-6})	727.308 (0.4841)	1.451 (1.0000)
15 [d]	2.81×10^{-6}	(2.65×10^{-6})	727.899 (0.6505)	0.860 (1.0000)
20	1.67×10^{-6}	(3.87×10^{-6})	728.598 (0.9227)	0.161 (1.0000)
25	1.48×10^{-6}	(5.19×10^{-6})	728.687 (0.9646)	0.072 (1.0000)
30	2.03×10^{-6}	(6.74×10^{-6})	728.680 (0.9613)	0.079 (1.0000)

[a] Deviance is -2 × Logarithm of the Likelihood. -2 × Ln (Likelihood) = 728.759 when beta = 0 (null model). The decrease in the deviance at a specific exposure lag (compared with the deviance at 0-years lag) has to be at least 3.84 for the improvement in the deviance to be statistically significant at the 5% significance level. The decrease in the deviance at a non-zero exposure lag (compared with the deviance for the null model) has to be at least 5.99 for the improvement in the deviance to be statistically significant at the 5% significance level.

[b] p-value vs null compares the maximum likelihood of the model fit to the maximum likelihood of the null model. A small p-value indicates that the model with the specified lag fits the data better than the null model.

[c] p-value vs zero lag compares the maximum likelihood of the model fit with the specified lag to the maximum likelihood of the model with zero lag. A small p-value indicates that the model with the specified lag fits the data better than the model with zero lag.

[d] Exposure lag ultimately used by USEPA (2016).

Table 8: Lymphoid Cell Lineage Tumor Mortality - NIOSH (male only) - MLE and SE of the Estimate for Different EtO Exposure Lags

Lag (years)	MLE	(SE)	Deviance [a]: -2 × Ln(Likelihood) (p-value vs null) [b]	Likelihood Ratio Test Statistic: Deviance (null model) – Deviance (model) (p-value vs zero lag) [c]
0	3.89×10^{-6}	(1.77×10^{-6})	354.312 (0.0696)	3.293 (n/a)
5	3.85×10^{-6}	(1.89×10^{-6})	354.761 (0.2412)	2.844 (1.0000)
10	3.47×10^{-6}	(2.17×10^{-6})	355.795 (0.4045)	1.810 (1.0000)
15 [d]	3.12×10^{-6}	(2.61×10^{-6})	356.553 (0.5910)	1.052 (1.0000)
20	1.63×10^{-6}	(4.08×10^{-6})	357.467 (0.9333)	0.138 (1.0000)
25	6.50×10^{-7}	(6.06×10^{-6})	357.594 (0.9945)	0.011 (1.0000)
30	1.70×10^{-6}	(8.66×10^{-6})	357.604 (0.9995)	0.001 (1.0000)

[a] Deviance is -2 × Logarithm of the Likelihood. -2 × Ln (Likelihood) = 357.605 when beta = 0 (null model). The decrease in the deviance at a specific exposure lag (compared with the deviance at 0-years lag) has to be at least 3.84 for the improvement in the deviance to be statistically significant at the 5% significance level. The decrease in the deviance at a non-zero exposure lag (compared with the deviance for the null model) has to be at least 5.99 for the improvement in the deviance to be statistically significant at the 5% significance level.

[b] p-value vs null compares the maximum likelihood of the model fit to the maximum likelihood of the null model. A small p-value indicates that the model with the specified lag fits the data better than the null model.

[c] p-value vs zero lag compares the maximum likelihood of the model fit with the specified lag to the maximum likelihood of the model with zero lag. A small p-value indicates that the model with the specified lag fits the data better than the model with zero lag.

[d] Exposure lag ultimately used by USEPA (2016).

Table 9: Lymphoid Cell Lineage Tumor Mortality - UCC/Dow 2013 update (males) - MLE and SE of the Estimate for Different EtO Exposure Lags

Lag (years)	MLE	(SE)	Deviance [a]: -2 × Ln (Likelihood) (p-value vs null) [b]	Likelihood Ratio Test Statistic: Deviance (null model) – Deviance (model) (p-value vs zero lag) [c]
0	-1.42×10^{-5}	(9.17×10^{-6})	299.443 (0.0592)	3.559 (n/a)
5	-1.50×10^{-5}	(9.44×10^{-6})	299.216 (0.1506)	3.786 (0.6338)
10	-1.58×10^{-5}	(9.74×10^{-6})	299.021 (0.1366)	3.981 (0.5159)
15 [d]	-1.60×10^{-5}	(9.94×10^{-6})	299.059 (0.1392)	3.943 (0.5355)
20	-1.52×10^{-5}	(9.91×10^{-6})	299.497 (0.1733)	3.505 (1.0000)
25	-1.53×10^{-5}	(1.03×10^{-5})	299.744 (0.1961)	3.258 (1.0000)
30	-1.51×10^{-5}	(1.07×10^{-5})	300.156 (0.2410)	2.846 (1.0000)

[a] Deviance is -2 × Logarithm of the Likelihood. -2 × Ln (Likelihood) = 303.002 when beta = 0 (null model). The decrease in the deviance at a specific exposure lag (compared with the deviance at 0-years lag) has to be at least 3.84 for the improvement in the deviance to be statistically significant at the 5% significance level. The decrease in the deviance at a non-zero exposure lag (compared with the deviance for the null model) has to be at least 5.99 for the improvement in the deviance to be statistically significant at the 5% significance level.
[b] p-value vs null compares the maximum likelihood of the model fit to the maximum likelihood of the null model. A small p-value indicates that the model with the specified lag fits the data better than the null model.
[c] p-value vs zero lag compares the maximum likelihood of the model fit with the specified lag to the maximum likelihood of the model with zero lag. A small p-value indicates that the model with the specified lag fits the data better than the model with zero lag.
[d] Exposure lag ultimately used by USEPA (2016).

In regard to Tables 7, 8, and 9, none of the EtO exposure lags result in a model that fits the NIOSH and UCC lymphoid cancer data statistically significantly better than the log-linear (Cox regression) model with no lag (at the 5% significance level). Aside from this statistical consideration, which does not give rise to a preference for any particular exposure lag duration, from a biological perspective it is reasonable to include an exposure lag of some duration to account for a latency period between exposure and cancer. *For this reason, as well as consistency with USEPA (2016), the TCEQ will also utilize an exposure lag of 15 years.*

3.4.1.5.1.2 Breast Cancer

Table 10 contains log-linear (standard Cox regression) model results for breast cancer mortality (female only) in the NIOSH cohort at various exposure lags.

Table 10: Breast Cancer Mortality - NIOSH (females) - MLE and SE of the Estimate for Different EtO Exposure Lags

Lag (years)	MLE	(SE)	Deviance [a]: -2 × Ln (Likelihood) (p-value vs null) [b]	Likelihood Ratio Test Statistic: Deviance (null model) – Deviance (model) (p-value vs zero lag) [c]
0	1.88×10^{-6}	(4.49×10^{-6})	1570.156 (0.6873)	0.162 (n/a)
5	2.89×10^{-6}	(4.56×10^{-6})	1569.958 (0.8353)	0.360 (0.6563)
10	3.49×10^{-6}	(4.94×10^{-6})	1569.879 (0.8029)	0.439 (0.5987)
15 [e]	6.01×10^{-6}	(5.12×10^{-6})	1569.211 (0.5749)	1.107 (0.3310)
20	9.42×10^{-6}	(5.48×10^{-6})	1568.171 (0.3418)	2.147 (0.1589)
25	1.22×10^{-5}	(6.73×10^{-6})	1567.998 (0.3135)	2.320 (0.1418)
30	1.63×10^{-5}	(8.56×10^{-6})	1567.791 (0.2826)	2.527 (0.1241) [d]

[a] Deviance is -2 × Logarithm of the Likelihood. -2 × Ln (Likelihood) = 1570.318 when beta = 0 (null model). The decrease in the deviance at a specific exposure lag (compared with the deviance at 0-years lag) has to be at least 3.84 for the improvement in the deviance to be statistically significant at the 5% significance level. The decrease in the deviance at a non-zero exposure lag (compared with the deviance for the null model) has to be at least 5.99 for the improvement in the deviance to be statistically significant at the 5% significance level.

[b] p-value vs null compares the maximum likelihood of the model fit to the maximum likelihood of the null model. A small p-value indicates that the model with the specified lag fits the data better than the null model.

[c] p-value vs lag compares the maximum likelihood of the model fit with the specified lag to the maximum likelihood of the model with zero lag. A small p-value indicates that the model with the specified lag fits the data better than the model with zero lag.

[d] Deviance for the model fit to breast cancer with exposures lagged 35 years is 1568.037 (not shown) so that the deviance does not continue to increase as the lag increases.

[e] Exposure lag ultimately used by USEPA (2016).

Regarding Table 10, the log-linear model did not fit the breast cancer *mortality* data statistically better than the null model (zero slope). However, it does fit the breast cancer *incidence* data better than the null model (see Table 4-14 in Appendix 5). Unfortunately, the NIOSH breast cancer incidence data were not publicly available for independent analysis. Therefore, the TCEQ

will not utilize Table 10 results, but rather consider log-linear (standard Cox regression) 15-year exposure-lagged model results for breast cancer incidence (subcohort with interviews) from USEPA (2016). Table 11 contains relevant results adapted from Table 4-12 of USEPA (2016).

Table 11: Breast Cancer Incidence (with interviews) - NIOSH (females) - MLE and SE of the Estimate [a]

Model	Lag (years)	MLE	(SE)
log-linear (standard Cox regression)	15	9.5×10^{-6}	4.1×10^{-6}

[a] Adapted from Table 4-12 of USEPA (2016).

3.4.1.5.2 Risk-Based Air Concentrations and URFs

3.4.1.5.2.1 Lymphoid Cancer

Consistent with the discussions above, 15-year lagged results are highlighted and bolded in Tables 12, 13, and 14 below, which contain environmental EtO air concentrations corresponding to the cited excess risk levels and associated URFs for lymphoid cancer mortality in the NIOSH (male + female), NIOSH (male only), and UCC (male only) cohorts, respectively. The lymphoid cancer calculations include adjustments for ADAFs using the approach described in Sielken and Valdez-Flores (2009).

Table 12: Lymphoid Cell Lineage Tumor Mortality - NIOSH (male + female) - MLE and 95% Lower Confidence Limit (95% LCL) of the Environmental EtO Concentration at 1 in 100,000 Excess Risk

Lag (years)	MLE Environmental Concentration (1/100,000 excess risk) ppm [a]	95% LCL Environmental Concentration (1/100,000 excess risk) ppm [a]	MLE URF per ppm	95% UCL URF per ppm
0	8.02×10^{-3}	4.30×10^{-3}	1.25×10^{-3}	2.32×10^{-3}
5	8.82×10^{-3}	4.57×10^{-3}	1.13×10^{-3}	2.19×10^{-3}
10	1.08×10^{-2}	4.93×10^{-3}	9.30×10^{-4}	2.03×10^{-3}
15 [b]	**1.32×10^{-2}**	**5.18×10^{-3}**	**7.57×10^{-4}**	**1.93×10^{-3}**
20	2.49×10^{-2}	5.18×10^{-3}	4.01×10^{-4}	1.93×10^{-3}
25	3.20×10^{-2}	4.73×10^{-3}	3.12×10^{-4}	2.11×10^{-3}
30	2.71×10^{-2}	4.19×10^{-3}	3.69×10^{-4}	2.38×10^{-3}

[a] Environmental concentration = (240 days/365 days) × (10 m^3/20 m^3) × occupational concentration.
[b] Exposure lag ultimately used by USEPA (2016).

Table 13: Lymphoid Cell Lineage Tumor Mortality - NIOSH (male only) - MLE and 95% LCL of the Environmental EtO Concentration at 1 in 100,000 Excess Risk

Lag (years)	MLE Environmental Concentration (1/100,000 excess risk) ppm [a]	95% LCL Environmental Concentration (1/100,000 excess risk) ppm [a]	MLE URF per ppm	95% UCL URF per ppm
0	5.83×10^{-3}	3.34×10^{-3}	1.71×10^{-3}	3.00×10^{-3}
5	6.43×10^{-3}	3.56×10^{-3}	1.56×10^{-3}	2.81×10^{-3}
10	7.84×10^{-3}	3.86×10^{-3}	1.28×10^{-3}	2.59×10^{-3}
15 [b]	**9.67×10^{-3}**	**4.07×10^{-3}**	**1.03×10^{-3}**	**2.46×10^{-3}**
20	2.08×10^{-2}	4.06×10^{-3}	4.81×10^{-4}	2.46×10^{-3}
25	5.94×10^{-2}	3.64×10^{-3}	1.68×10^{-4}	2.75×10^{-3}
30	2.64×10^{-2}	2.81×10^{-3}	3.79×10^{-4}	3.56×10^{-3}

[a] Environmental concentration = (240 days/365 days) × (10 m^3/20 m^3) × occupational concentration.
[b] Exposure lag ultimately used by USEPA (2016).

Table 14: Lymphoid Cell Lineage Tumor Mortality - UCC/DOW 2013 Update (males) - MLE and 95% LCL of the Environmental EtO Concentration at 1 in 100,000 Excess Risk

Lag (years)	MLE Environmental Concentration (1/100,000 excess risk) ppm [a]	95% LCL Environmental Concentration (1/100,000 excess risk) ppm [a]	MLE URF per ppm	95% UCL URF per ppm
0	n/a [c]	2.59×10^{-2}	0	3.86×10^{-4}
5	n/a	4.76×10^{-2}	0	2.10×10^{-4}
10	n/a	1.24×10^{-1}	0	8.06×10^{-5}
15 [b]	**n/a**	**8.70×10^{-2}**	**0**	**1.15×10^{-4}**
20	n/a	3.08×10^{-2}	0	3.25×10^{-4}
25	n/a	2.35×10^{-2}	0	4.25×10^{-4}
30	n/a	1.79×10^{-2}	0	5.58×10^{-4}

[a] Environmental concentration = (240 days/365 days) × (10 m^3/20 m^3) × occupational concentration.
[b] Exposure lag ultimately used by USEPA (2016).
[c] n/a implies that the estimated dose-response relationship was non-increasing.

For lymphoid cancer in the NIOSH cohort (male + female), Table 12 provides an EtO air concentration of 13.2 ppb (1.32E-02 ppm) as corresponding to a no significant excess risk level of 1 in 100,000 based on the MLE for the cohort (15-year exposure lag). Based on the 95% LCL (i.e., LEC_{01}), 5.2 ppb (5.18E-03 ppm) is the EtO air concentration corresponding to a 1 in 100,000 excess risk. *These lymphoid cancer excess risk results are consistent with TCEQ conclusions regarding the range of EtO air concentrations most likely to be associated with excess risk considering normal endogenous levels* (see Sections 3.4.1.2.1 and 3.4.1.4.1). For example, a continuous EtO air concentration ≥ ≈4.6-7 ppb would itself produce an internal exposure above the normal endogenous range and is considered most likely to be associated with excess (i.e., above and distinguishable from background) risk. Thus, the range of 5.2-13.2 ppb for a 1 in 100,000 excess risk is considered biologically plausible considering normal background endogenous levels. Even at a 1 in 1,000,000 excess risk level, the upper end of the corresponding EtO air concentration range (1.32 ppb) would also correspond to a 1 SD increase in internal exposure over normal endogenous levels, which is predicted to be sufficient to move those at the 90th percentile of normal background endogenous levels to over the 95th percentile (Table 4 of Kirman and Hays 2017). This would be a statistically significant increase and could be potentially biologically meaningful/significant (see Section 3.4.1.2.1). Additionally, unlike the USEPA (2016) URF for lymphoid cancer incidence, use of the URFs corresponding to the MLE (7.57E-07 per ppb) and 95% UCL (1.93E-06 per ppb) along with the EtO air concentrations corresponding to the means of background levels in the unexposed population (1.9 ppb) and smokers (18.8 ppb) does not predict a nonsmoker/smoker population-weighted background rate of lymphoid cancer mortality above the actual applicable background rate (e.g., 0.53% for lymphoid cancer mortality, male + female, 70-year lifetime). *Accordingly, based on normal endogenous/background levels and this URF reality check, the TCEQ considers these 1 in 100,000 excess risk level EtO air concentrations as both biologically plausible and scientifically reasonable, and therefore has some confidence in them*. Results are similar for NIOSH males only. That is, Table 13 provides MLE and 95% LCL 1 in 100,000 excess risk EtO air concentrations of 9.7 ppb (9.67E-03 ppm) and 4.1 ppb (4.07E-03 ppm), respectively.

For lymphoid cancer in the UCC cohort (males), Table 14 provides an EtO air concentration of 87 ppb (8.70E-02 ppm) that corresponds to a no significant excess risk level of 1 in 100,000 based on the 95% LCL for the cohort (15-year exposure lag), which is 6.6 times higher than the corresponding value based on the NIOSH cohort (males + females). No MLE value is provided because of the negative value in Table 9, consistent with no increased risk with cumulative EtO exposure for the cohort as modeled and reported. The 87 ppb EtO concentration corresponding to a 1 in 100,000 excess risk level for lymphoid cancer (based on the 95% LCL) for the UCC cohort is well above the lower end of the range of continuous EtO air concentrations (≥ ≈4.6-7 ppb) that would itself produce internal exposures above the normal endogenous range, and an EtO air concentration above this range is considered most likely to be associated with excess (i.e., above and distinguishable from background) risk. Even at a 1 in 1,000,000 excess risk level,

the corresponding EtO air concentration (8.7 ppb) would also correspond to an increase in internal exposure predicted to be greater than the upper end of the normal endogenous range (Table 4 of Kirman and Hays 2017). Thus, considering normal background endogenous levels, it is biologically plausible that such a change would be associated with excess risk. Additionally, unlike the USEPA (2016) URF for lymphoid cancer incidence, use of the URF corresponding to 95% UCL (1.15E-07 per ppb) along with the EtO air concentrations corresponding to the means of background levels in the unexposed population (1.9 ppb) and smokers (18.8 ppb) does not predict a nonsmoker/smoker population-weighted background rate of lymphoid cancer mortality above the actual applicable background rate (e.g., 0.65% for lymphoid cancer mortality, males only, 70-year lifetime). Accordingly, based on normal endogenous/ background levels and this URF reality check, the TCEQ considers excess risk at this air concentration as both biologically plausible and scientifically reasonable.

However, the fact that the associated MLE, which represents the best fit to the data (i.e., by definition, the MLE maximizes the likelihood of the observed data), *is consistent with no excess lymphoid cancer mortality risk for the UCC cohort*:

- Suggests that the use of statistical bound results (95% LCL/UCL) for estimating excess risk for both the UCC cohort and other populations (e.g., the general population) may be conservative; and
- Similarly, as part of the weight of evidence, suggests that use of lymphoid cancer excess risk results based on the NIOSH cohort for extrapolation to other populations, even highly exposed occupational populations, may be conservative (especially use of the 95% upper statistical bound on excess risk).

This is further supported by the fact that *none of the slopes for lymphoid mortality in the NIOSH cohort (male + female, male only) or UCC cohort (males) are statistically significantly greater than zero* (at the 5% significance level). Thus, *any excess risk estimates based on these lymphoid cancer analyses may be considered conservative and health-protective*, particularly if the 95% UCL URF is utilized for calculation of the EtO air concentration corresponding to 1 in 100,000 excess risk.

3.4.1.5.2.2 Breast Cancer

Table 15 contains environmental EtO air concentrations corresponding to the cited excess risk level and associated URFs for breast cancer incidence in the NIOSH (female only) cohort.

Table 15: Breast Cancer Incidence (with interviews) - NIOSH (females) - MLE and 95% LCL of the Environmental EtO Concentration at 1 in 100 Excess Risk [a]

Model	Lag (years)	EC_{01} ppm	URF per ppm [b]	LEC_{01} ppm [c]	URF per ppm [b]
log-linear (standard Cox regression)	15	0.126	7.94×10^{-2}	0.0737	1.36×10^{-1}

[a] Adapted from Table 4-15 of USEPA (2016).
[b] URF = 0.01/ EC_{01} or LEC_{01}.
[c] Confidence intervals used in deriving the LEC_{01} was estimated employing the Wald approach for the log-linear RR models.

For breast cancer incidence, the MLE URF (7.94E-05 per ppb) in Table 15 corresponds to an EtO air concentration of 0.13 ppb for a no significant excess risk level of 1 in 100,000 based on females in the NIOSH cohort (15-year exposure lag). Based on the 95% UCL URF (1.36E-04 per ppb), 0.074 ppb is the EtO air concentration corresponding to a 1 in 100,000 excess risk. *These breast cancer incidence excess risk results are not consistent with TCEQ conclusions regarding the range of EtO air concentrations likely to be associated with excess risk considering normal endogenous EtO levels* (see Sections 3.4.1.2.1 and 3.4.1.4.1). For example, the EtO air concentration corresponding to the mean endogenous level in the unexposed population is 1.9 ppb, and continuous exposure to 0.074-0.13 ppb EtO is predicted to correspond to an increase of only ≈6-10% of the SD for normal endogenous levels; a deviation well within the range of normal endogenous variation in the unexposed population (Table 4 of Kirman and Hays 2017). For additional perspective, the cumulative exposure associated with a lifetime of environmental exposure to 0.074-0.13 ppb (≈1.9-3.3 ppm × days) is >4,430-7,695 times less than the lowest cumulative exposure levels associated with a statistical increase in breast cancer incidence in the NIOSH cohort (>14,620 ppm-days, 15-year lagged exposure; Table 5). *The TCEQ finds no basis to conclude that the resulting change in internal dose from continuous exposure to 0.074-0.13 ppb EtO would be biologically meaningful/significant, or from a biological plausibility perspective, would be expected to result in excess risk* (i.e., above and distinguishable from normal endogenous EtO contributions to background risk*).* The TCEQ is not confident in the scientific reasonableness of these excess risk results for breast cancer incidence.

3.4.1.6 Selection of Critical Cancer Endpoint and Final URF

3.4.1.6.1 Critical Cancer Endpoint

As discussed above, lymphoid cancer mortality excess risk results are consistent with the range of EtO air concentrations expected to most likely be associated with excess risk. *The TCEQ considers the 1 in 100,000 excess risk level EtO air concentrations for lymphoid cancer based on Cox proportional hazards modeling (15-year exposure lag) to be both biologically plausible and scientifically reasonable, thereby increasing confidence in their use for regulatory purposes*. For

example, unlike the USEPA (2016) URF for lymphoid cancer incidence, use of the URFs corresponding to the MLE (7.57E-07 per ppb) and 95% UCL (1.93E-06 per ppb) for the full NIOSH cohort (male + female) along with the EtO air concentrations corresponding to the means of background levels in the unexposed population (1.9 ppb) and smokers (18.8 ppb) does not predict a nonsmoker/smoker population-weighted background rate of lymphoid cancer mortality above the actual applicable background rate (e.g., 0.53% for lymphoid cancer mortality, male + female, 70-year lifetime). *By contrast, the TCEQ lacks confidence in the scientific reasonableness of excess risk results for breast cancer incidence* (e.g., exposure to the calculated 1 in 100,000 excess risk EtO air concentrations would result in internal exposures well within the range of normal endogenous variation of nonsmokers). Consequently, after due consideration of both cancer endpoints, *the TCEQ ultimately selects lymphoid cancer as the critical cancer endpoint for derivation of the EtO URF.*

3.4.1.6.2 Final URF and Air Concentrations at 1 in 100,000 Excess Risk

For lymphoid tumors, Tables 12, 13, and 14 contain URFs and 1 in 100,000 excess risk EtO air concentrations based on the NIOSH (male + female), NIOSH (male only), and UCC (males) cohorts, respectively. *For protection against lymphoid tumors, a value based on males is considered most conservative as the lymphoid tumor slope for females in the NIOSH cohort was not positive* (denoted by "-ns" in Table 6). For example, the URF (MLE) for NIOSH (male + female) is 7.57E-07 per ppb (15-year lag; Table 12) whereas the URF (MLE) for NIOSH (males only) is 1.03E-06 per ppb (15-year lag; Table 13), which is 36% higher. *When determining the final EtO URF, the weighting of data from both cohorts (NIOSH and UCC) must be considered.* For example, in TCEQ's (2011) assessment of the carcinogenicity for nickel a weighting factor of person-years × $1/SE^2$ was used to combine URFs. Similarly, in the carcinogenic assessment of inorganic arsenic (TCEQ 2012), the inverse of the variance ($1/SE^2$) for the β (MLE) was used to weight URFs for the final URF. Inverse-variance weighting (without a person-years weighting factor) is a more standard statistical procedure used in meta-analyses.

SE values for the slopes were obtained from Tables 8 and 9 (15-year lag) for the Cox proportional hazards model evaluation of lymphoid tumors in NIOSH males (SE=2.61E-06) and UCC males (SE=9.94E-06), respectively. For comparison, it is noted that the SE (2.65E-06; Table 7) for the full NIOSH cohort (male + female) provides similar weighting results. Both types of weighting factors previously used by the TCEQ were calculated (i.e., $1/SE^2$ and person-years × $1/SE^2$) and are provided in Table 16.

Table 16: Weighting Factors for the Lymphoid Tumor Analyses for the NIOSH and UCC Cohorts

Cohort	Gender	Slope SE	Weight $1/SE^2$	Weight Ratio NIOSH/ UCC	Person-Years	Total Weight Person-Years × $1/SE^2$	Relative Total Weight NIOSH/ UCC
NIOSH	M	2.61E-06	1.47E+11	14.5	189,868	2.79E+16	33.0
NIOSH	M/F	2.65E-06	1.42E+11	14.1	450,906	6.42E+16	76.0
UCC	M	9.94E-06	1.01E+10		83,524	8.45E+14	

As seen from Table 16, using person-years × $1/SE^2$ as a weighting factor results in the NIOSH (males only) cohort receiving ≥33-fold greater weight than the UCC (males) cohort. Aside from consideration of cohort person-years or the number of cohort cancer mortalities observed, using $1/SE^2$ as a weighting factor produces qualitatively similar results, with the NIOSH (males only) cohort receiving >10-times more weight than the UCC (males) cohort. *Thus, based on the considerations inherent to the weighting factors applied, results suggest that for all practical purposes the URF (and corresponding 1 in 100,000 excess risk air concentration) should be based on the NIOSH cohort*.

In accordance with the considerations discussed above, the final EtO URF for lymphoid cancer will be based on the NIOSH (males only) cohort (15-year lagged exposure). *Furthermore, as both a scientifically reasonable and conservative selection, the URF (95% UCL) of 2.5E-06 per ppb will serve as the final URF for lymphoid tumors (Table 13).*

EtO Lymphoid Cancer URF = 2.5E-06 per ppb or 1.4E-06 per µg/m^3

The corresponding 1 in 100,000 excess risk EtO air concentration for lymphoid tumors is 4 ppb or 7 µg/m^3 (i.e., 1E-05/2.5E-06 per ppb = 4.0 ppb × 1.83 µg/m^3/ppb = 7.3 µg/m^3). As indicated previously (Section 3.4.1.5.2.1), these results incorporate USEPA (2005b) ADAFs in consideration of the MOA analysis and the potential for increased early-life susceptibility. A lymphoid cancer 1 in 100,000 excess risk EtO air concentration value based on the full NIOSH (male + female) cohort would be somewhat higher at 5.2 ppb, but within a factor of 1.3. Similarly, based on the URF (MLE) values, EtO air concentrations corresponding to 1 in 100,000 excess risk for both the NIOSH (male + female) full cohort and NIOSH (males only) cohort would be somewhat higher at 13.2 ppb and 9.7 ppb, respectively (Tables 12 and 13). As stated previously, EtO air concentrations that themselves produce internal exposures above the normal endogenous range (e.g., continuous air exposure concentrations ≥ ≈4.6-7 ppb) are considered most likely to be associated with excess (i.e., above background) risk, and the TCEQ notes that these calculated risk-based air concentrations for lymphoid tumors are remarkably consistent with this expectation.

For additional context, continuous exposure to 4 ppb EtO would be predicted to result in an HEV burden (as a biomarker of internal exposure) of approximately 43.6 pmol/g Hb. This HEV level roughly approximates the mean +1 SD (21.1 + 14.6 pmol/g Hb = 35.7 pmol/g Hb) of the normal distribution in the non-smoking population that results from endogenous EtO exposure (Table 4 of Kirman and Hays 2017). An additional ≈43.6 pmol/g Hb due to continuous exogenous exposure to 4 ppb would be predicted to:

- Increase the HEV level for the median non-smoker to between the 95th and 99th percentiles of normal endogenous background levels; and
- Increase the HEV level in 90th percentile non-smokers to over the 99th percentile.

An exogenous EtO exposure concentration that results in endogenous levels rising above the normal background range in some appreciable portion of the population (e.g., the 90th percentile to > 99th percentile) is considered consistent with the assessment of "excess" (i.e., above background) risk. By contrast, continuous exposure to 0.001 ppb EtO (i.e., the 1 in 100,000 excess risk air concentration using USEPA's URF) would result in ≈0.0109 pmol/g Hb added HEV, a mere 0.075% of the SD for normal background endogenous levels and over 360 times less than even the 1st percentile of normal background endogenous levels - this magnitude of change in HEV may be reasonably characterized as biologically insignificant. Extremely low air concentrations corresponding to internal exposure increases that represent such minuscule, *de minimus* fractions of normal endogenous background levels do not provide a scientific basis, much less a robust one, for the biological or mechanistic plausibility of any appreciable excess (i.e., above background) risk. In fact, it suggests the opposite due to the body's inherent ability to deal with typical endogenous levels through normal detoxification and repair processes.

Thus, based on the data evaluated and considerations discussed, an EtO **$^{chronic}ESL_{nonthreshold(c)}$ of 4 ppb** is considered health-protective, scientifically reasonable, and relatively consistent with the assessment of excess risk as being above and distinguishable from normal endogenous EtO contributions to background risk. Continuous exposure to 4 ppb EtO would be predicted to correspond to internal exposure level increases to or above the upper end of the range (e.g., 95th-99th percentile) of normal endogenous levels at least for some percentage of the population (e.g., those at ≈90th percentile). Additionally, as shown in Appendix 3, the Cox proportional hazards model assessment used by the TCEQ (log-linear, 15-year exposure lag, 95% UCL) neither statistically over- or under-predicts the lymphoid cancer numbers observed in the NIOSH cohort. The calculated EtO $^{chronic}ESL_{nonthreshold(c)}$ (4 ppb) falls within the range (0.13-6.9 ppb) supported by the approach in Kirman and Hays (2017) as protective of human health, and is conservative (60-87% lower) compared to that proposed by Valdez-Flores et al. (2010) at the 1 in 100,000 excess risk level (i.e., 1-3 ppb at 1E-06 ≈ 10-30 ppb at 1E-05 compared to 4 ppb). Lastly, it is simply noted that the European Commission's Scientific Committee on Occupational

Exposure Limits has adopted the same modeling approaches of Valdez-Flores et al. for EtO cancer assessment (SCOEL 2012, Valdez-Flores et al. 2011).

3.4.2 Evaluating Susceptibility from Early-Life Exposures

Per Section 3.3.1, the weight of evidence supports a mutagenic MOA for EtO carcinogenicity. The mutagenic MOA is considered relevant to all populations and life stages. See Section 3.5.2 of USEPA (2016) for available information on potentially susceptible life stages and populations (e.g., those with higher HEV adduct levels due to a null GSTT1 genotype or with DNA repair deficiencies). USEPA (2016) indicates that there are no data on the relative susceptibility of children to EtO (e.g., the potential for decreased detoxification/clearance by hydrolysis as a primary metabolic pathway and/or glutathione conjugation). In the absence of chemical-specific data to evaluate potential child/adult differences in susceptibility, USEPA (2005b) provides default ADAFs to account for potentially increased susceptibility in children due to early-life exposure when a chemical has been identified as acting through a mutagenic MOA. Therefore, because of the weight of evidence supporting a mutagenic MOA and the lack of chemical-specific data on potential differences in susceptibility, increased early-life susceptibility should be assumed and ADAFs applied (TCEQ 2015). As previously mentioned, the results utilized by the TCEQ (e.g., Table 13) already inherently incorporate USEPA (2005b) ADAFs. As such, no further adjustments are necessary.

3.4.3 Final EtO URF and $^{chronic}ESL_{nonthreshold(c)}$

3.5 Long-Term ESL and Value for Air Monitoring Evaluation

The chronic evaluation resulted in the derivation of the following values for EtO:

- $^{chronic}ESL_{nonthreshold(c)}$ = 7 µg/m^3 (4 ppb) (rounded to one significant figure)
- URF = 1.4E-06 per µg/m^3 (2.5E-06 per ppb) for lymphoid cancer

The long-term ESL for air permit reviews and the evaluation of long-term ambient air monitoring data, set at an excess risk of 1 in 100,000, is the $^{chronic}ESL_{nonthreshold(c)}$ of 7 µg/m^3 (4 ppb). The URF is 2.5E-06 per ppb for lymphoid cancer or 1.4E-06 per µg/m^3 (see Section 3.4.1.6.2).

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